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ORIGINAL ARTICLE

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Direct oral anticoagulant plasma levels and thrombin generation on ST Genesia system

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Abstract

Background: Monitoring of anticoagulant activity of direct oral anticoagulants (DOACs) can be necessary in special situations. DOAC plasma levels have a high inter- and intraindividual variation and do not necessarily reflect the coagulation status of the patient. Thrombin generation (TG) is a global hemostatic assay with the capacity to overcome this limitation. The aim of this study was to show correlations between DOAC plasma levels and TG parameters using the fully automated ST Genesia system.

Methods: A total of 380 blood samples (120 with apixaban, 79 with dabigatran, 79 with edoxaban, and 102 with rivaroxaban) from patients at different time points after DOAC intake were included in the analysis. DOAC plasma levels were analyzed using calibrated anti-Xa or anti-IIa tests. Thrombin generation was measured using the ST Genesia system and STG-DrugScreen reagent.

Results: There was a significant correlation between the drug levels of all DOACs and the TG parameters' lag time and time to peak. Peak thrombin and velocity index show a negative correlation following an exponential regression curve with all anti-Xa DOACs but not with dabigatran. Apart from a weak correlation with rivaroxaban, there was no correlation between drug levels of all other DOACs and endogenous thrombin potential.

Conclusion: TG parameters measured with ST Genesia correlate with the drug levels of anti-Xa DOACs. Peak thrombin and velocity index are of special interest for the determination of residual anticoagulant effect at low drug levels. For dabigatran-treated patients, only lag time shows a correlation with the dabigatran plasma levels.

KEYWORDS

anti-Xa-inhibitors, correlation, dabigatran, DOAC plasma levels, ST Genesia, thrombin generation

Christian Pfrepper and Michael Metze contributed equally to this work.

Essentials

- The correlation of thrombin generation (TG) with direct oral anticoagulants (DOAC) is not known.
- TG parameters were correlated with plasma levels from 112 DOAC-treated patients.
- TG parameters' lag time and time to peak were sensitive to plasma levels of all DOACs.
- Apixaban, edoxaban, and rivaroxaban drug levels correlate with peak thrombin and velocity index.

1 | INTRODUCTION

Direct oral anticoagulants (DOACs) are currently licensed for stroke prevention in nonvalvular atrial fibrillation and for the treatment of venous thromboembolism.[1,2] Routine monitoring is not necessary, as DOACs do not require dose adjustments based on plasma levels. However, the measurement of DOAC plasma levels can be required in special situations such as bleedings or thromboembolic events on anticoagulation or in case of a planned reversal of anticoagulation.[3-5] Chromogenic or clotting tests calibrated to each DOAC have been introduced for the measurement of DOAC plasma levels. Although recommendations for the standardization of laboratory test for DOACs have been published,[5,6] the inter- and intraindividual variation of DOAC plasma levels remains high, and it does not necessarily reflect the real coagulation status of the patient.

Thrombin generation assay (TGA) is a global hemostatic assay measuring the concentration of thrombin over time. Currently available instruments for the measurement of thrombin generation (TG) include the Innovance ETP (Siemens Healthcare), Technothrombin TGA (Technoclone) and the Thrombinoscope calibrated automated thrombogram (CAT; Diagnostica Stago). The main disadvantage of TGAs is the poor standardization, lack of quality controls, and the high interlaboratory variations.[7-10]

The ST Genesia is a fully automated system for the measurement of TG. It is standardized and designed for the introduction of TG into the clinical routine. It has recently been shown that ST Genesia offers excellent interexperimental precision by using a reference plasma.[11] The aim of this study was to provide data on ST Genesia measurements in correlation with DOAC plasma levels in patients under treatment with apixaban, rivaroxaban, edoxaban, and dabigatran.

2 | METHODS

2.1 | Patient population

This study includes 2 cohorts of patients.

Cohort 1 consisted of 80 patients on DOAC treatment for atrial fibrillation or venous thromboembolism, with 20 patients for each DOAC. The patients received the full anticoagulant dose (5 mg apixaban, 60 mg edoxaban, 20 mg rivaroxaban, and 150 mg dabigatran). Patients newly started on DOAC treatment or in whom the DOAC was discontinued for a minimum of 48 hours for elective coronary angiography or cardiac device implantation were eligible. Exclusion criteria were aged <18 years, lack of informed consent, current pregnancy and lactation, autoimmune disease, severe anemia (hemoglobin <8 g/dL or <5.0 mmol/L), or sepsis. Blood was obtained before as well as 3, 6, and 12 hours after intake of the DOAC.

Cohort 2 consisted of 20 patients on stable treatment with apixaban and 13 patients on stable treatment with rivaroxaban, who were managed in our coagulation outpatient service. Blood was drawn 10-14 hours after the last intake of apixaban and 22-26 hours after last intake of rivaroxaban (trough level) and 3-4 hours after the intake of the DOAC (peak level).

2.2 | Sample collection and processing

Blood samples were collected in citrated vacuum containers via venipuncture. No indwelling catheters were used. Blood was centrifuged at 4000 rpm (1800 *g*) for 2-10 minutes to prepare platelet-poor plasma, aliquoted and stored at −80°C until the analysis was performed. DOAC levels were measured with the STA-liquid Anti-Xa (Diagnostica Stago) and the corresponding STA-Apixaban, STA-Rivaroxaban and STA-Edoxaban Calibrator reagents. Dabigatran plasma levels were measured using diluted Hemoclot thrombin time with the corresponding calibrator (Hyphen Biomed). All measurements were performed using the BCS analyzer (Siemens Healthineers).

TG was assessed with the ST Genesia analyzer using STG-DrugScreen reagent (Diagnostica Stago) according to manufacturer's instruction The principle of the determination of TG with the fully automated and standardized ST Genesia system is similar to the semi-automated CAT[12] with differences in temperature control and calibration.[13] Dedicated reagents, calibrators, quality controls, and reference plasmas are used in the ST Genesia. STG-DrugScreen contains a mixture of phospholipids, recombinant tissue factor (TF) at a relatively high picomolar concentration and uses human thrombin in buffer for calibration. Detailed information about TG measurement with ST Genesia have been previously described.[11,13]

2.3 | Statistical analysis

Spearman's correlations coefficient *r* and *P* values were determined using linear regression model for the correlation between DOAC levels and TG parameters. Mandel's test was used to decide whether the scatter diagram fits a linear model. In case a nonlinear model had to be selected, the best fit model was selected and the regression was displayed as R^2 in the graph. *P* values < .05 were considered significant. Sensitivity, specificity, positive

predictive value (PPV) and negative predictive value (NPV) for the combination of TG parameters within the range of untreated patients to predict DOAC levels < 30 ng/mL and <50 ng/mL were calculated as previously described.[14] These thresholds were chosen because the ISTH recommends antidote administration prior to urgent interventions associated with a high bleeding risk for DOAC levels > 30 ng/mL and in case of serious bleedings for DOAC levels >50 ng/mL.[15] Sensitivity was defined as the percentage of patients with DOAC levels below 30 or 50 ng/mL having TG values within the reference range. Specificity was defined as the percentage of patients with DOAC levels above 30 or 50 ng/mL having TG parameters outside the reference range. PPV was the probability that patients with TG parameters within the reference range have a DOAC level below 30 or 50 ng/mL and NPV the probability that patients with TG parameters outside the reference range have DOAC levels above 30 or 50 ng/mL. The average detection limit was defined as the drug level in ng/mL at which the regression line crosses the upper limit of normal for lag time and time to peak (TTP) and the lower limit of normal for peak thrombin and velocity index. The maximum detection limit was defined as the drug level in nanograms per milliliter at which all values for lag time and TTP are below and for peak thrombin and velocity index above the normal range. Data were analyzed using IBM SPSS version 22 and Microsoft Office Excel.

2.4 | Ethical considerations

The study was approved by the ethics committee of the University of Leipzig (reference 207/16-ek for cohort 1, reference 163/17-ek for cohort 2) and performed according to the Declaration of Helsinki. Informed consent was obtained from all study participants before inclusion. Inclusion in the study had no impact on the anticoagulation management of the patients.

3 | RESULTS

A total of 380 blood samples (120 with apixaban from 40 patients, 79 with edoxaban from 20 patients, 79 with dabigatran from 20 patients, and 102 with rivaroxaban from 32 patients) were included in the analysis.

According to Mandel's test, linearity was shown only for lag time with apixaban and edoxaban and for endogenous thrombin potential (ETP) with all DOACs.

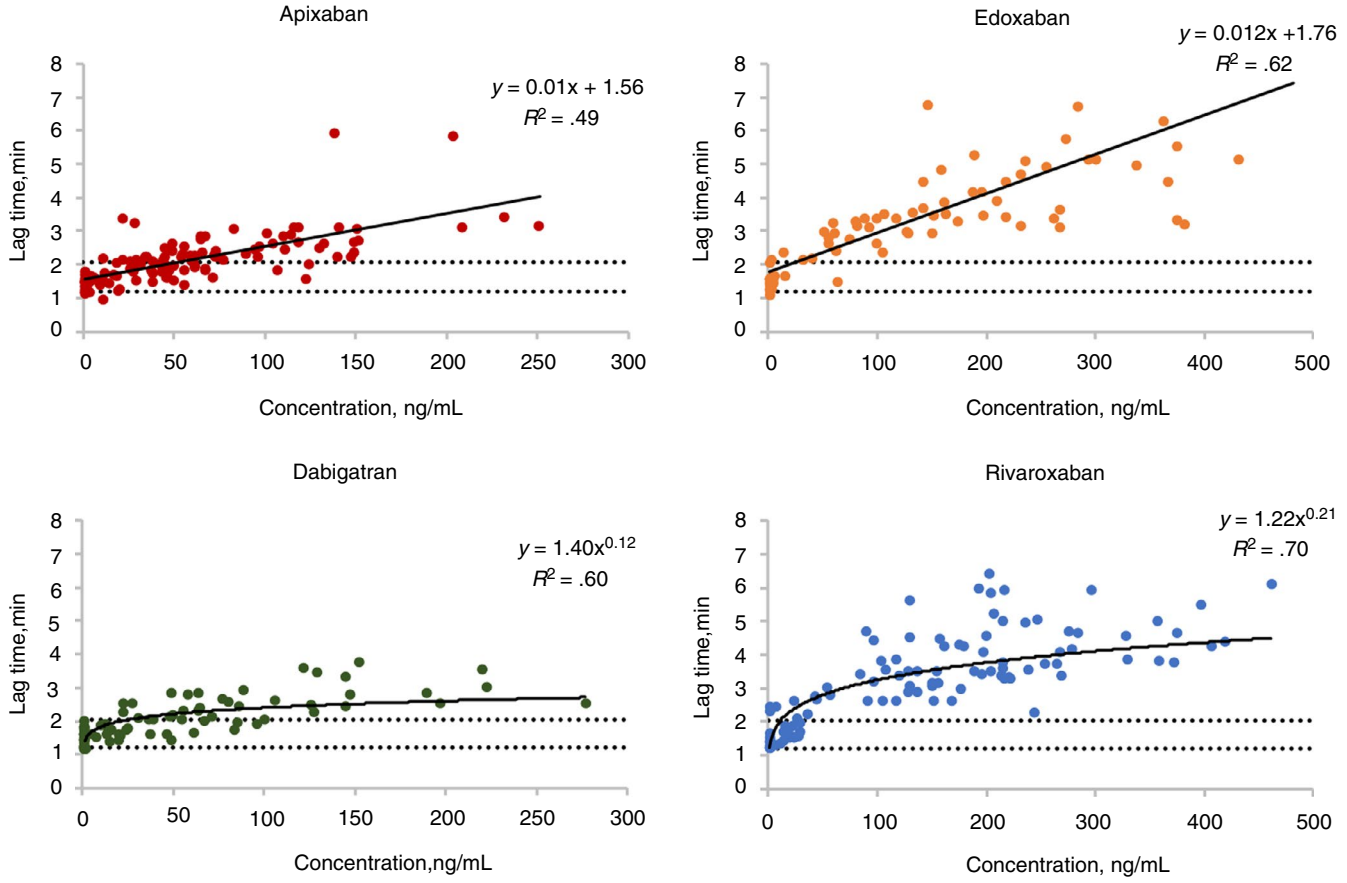

FIGURE 1 Correlation between direct oral anticoagulant (DOAC) concentrations and thrombin generation lag time. For better visualization, *y* axis was adjusted to a maximum of 8 min. Two outliers in the same patient from the edoxaban group were not included in the figure (drug level 238 ng/mL, lag time 8.8 min and drug level 482 ng/mL, lag time 12.7 min). Solid line: regression curve; dotted lines: 2.5 and 97.5th percentile of 42 untreated patients

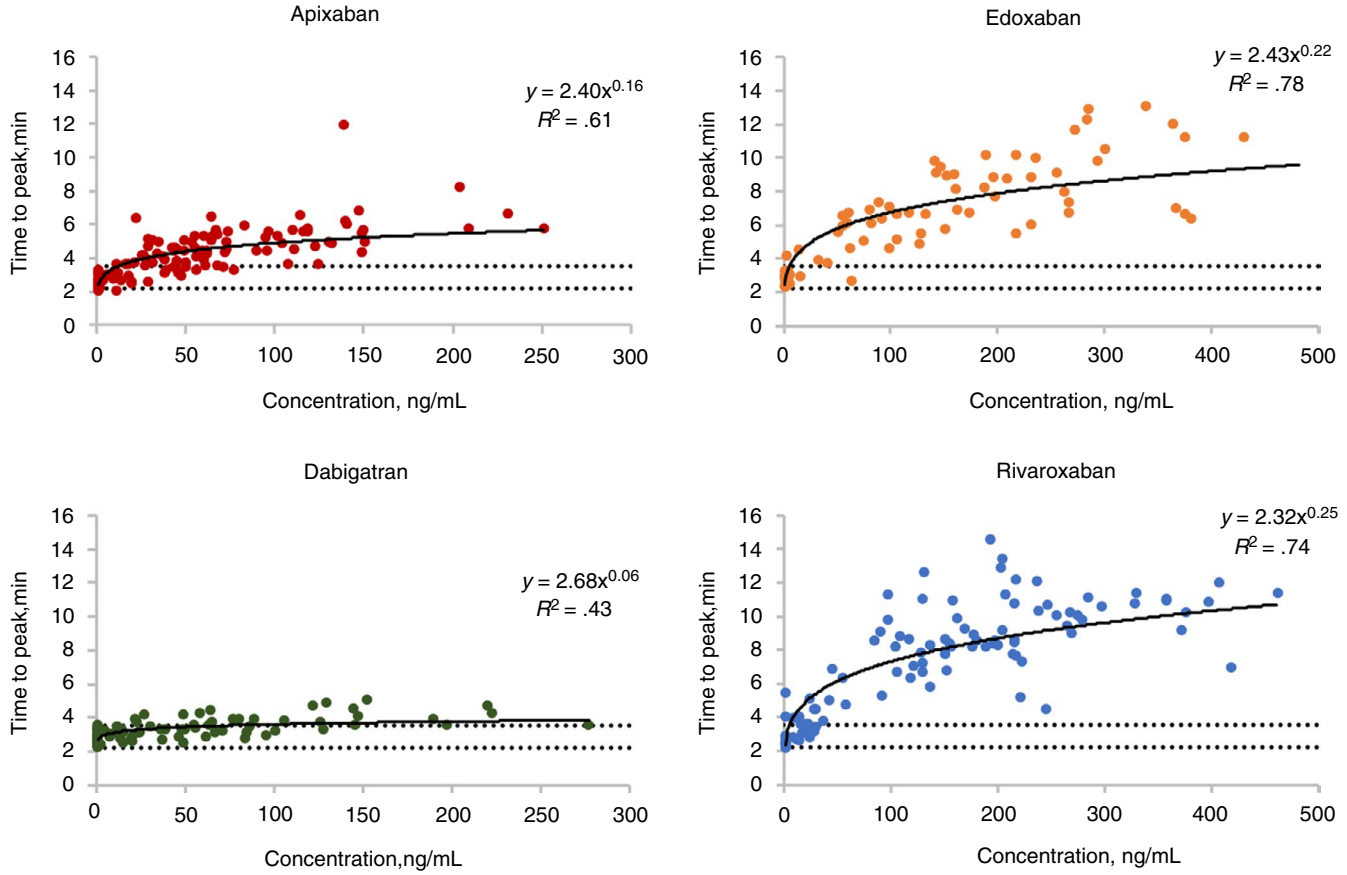

FIGURE 2 Correlation between direct oral anticoagulant (DOAC) concentrations and time to peak thrombin generation. For better visualization, *y* axis was adjusted to a maximum of 16 min. One outlier in the edoxaban group was not included in the figure (drug level 482 ng/mL, time to peak 17.1 min). Solid line: regression curve; dotted lines: 2.5th and 97.5th percentile of 42 untreated patients

3.1 | Baseline TG parameters

To determine the baseline TG parameters, we selected plasma samples from 42 untreated patients from cohort 1 before the DOAC therapy was newly started. Mean (2.5th-97.5th percentile) TG parameters of these 42 patients were lag time, 1.50 (1.19-2.06) min; TTP, 2.79 (2.24-3.56) min; thrombin peak, 448 (323-674) nmol/L; ETP, 1803 (1129-3211) nmol/L*min; velocity index, 517 (268-769) nmol/min.

3.2 | Lag time

There was a significant linear correlation between lag time and all DOACs, with a correlation coefficient of >.78 for all DOACs (Figure 1).

3.3 | Time to peak

Correlation between drug levels and TTP was higher for anti-Xa-DOACs than for dabigatran (Figure 2).

3.4 | Peak thrombin

There was a significant negative nonlinear correlation between the drug levels and peak thrombin in all anti-Xa DOACs. In contrast, this correlation was not significant for dabigatran (r = −.195, P = .086) (Figure 3).

3.5 | Endogenous thrombin potential

Spearman correlation for rivaroxaban drug levels with ETP was −0.326 (P = .001). Apart from this, there was no correlation between the drug levels of any DOAC and ETP (Figure 4).

3.6 | Velocity index

Drug levels of anti-Xa-DOACs showed a significant negative correlation with velocity index, while this correlation was not significant for dabigatran (Figure 5).

Correlations between drug levels of all DOACs and TG parameters are summarized in Table 1.

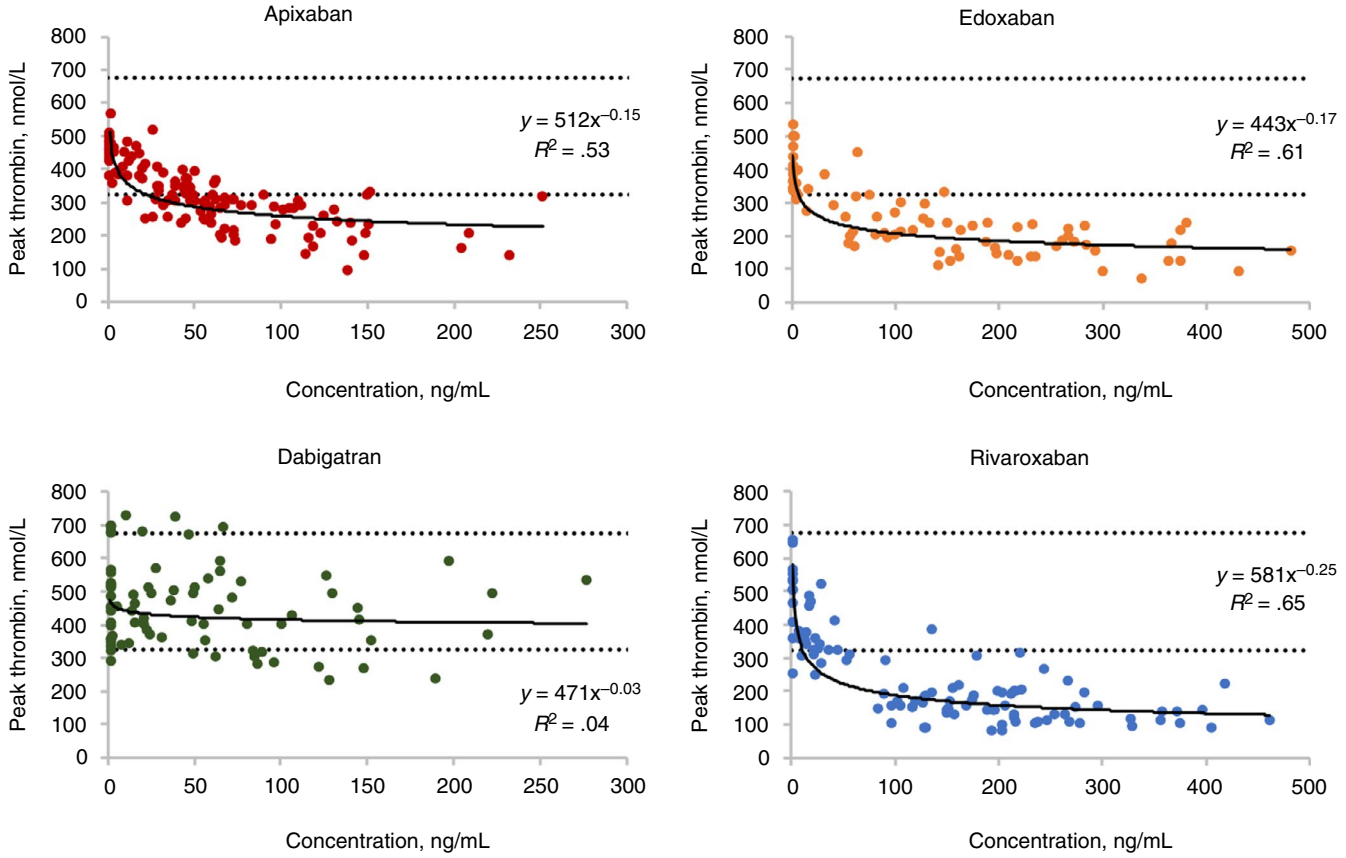

FIGURE 3 Correlation between direct oral anticoagulant (DOAC) concentrations and peak thrombin generation. Solid line: regression curve; dotted lines: 2.5th and 97.5th percentile of 42 untreated patients

3.7 | Sensitivity, specificity, and detection limits

Prediction of DOAC levels <30 ng/mL: The sensitivity of the TG parameters' lag time and peak thrombin to predict DOAC levels <30 ng/mL was >80% for all DOACs, but the specificity was >80% only for edoxaban and rivaroxaban. The PPV was > 90% for lag time, TTP, and velocity index in patients treated with edoxaban and rivaroxaban, but it was <80% for apixaban and dabigatran. The NPV was >85% for all TG parameters and all DOACs, except for the combination of dabigatran and velocity index.

Prediction of DOAC levels <50 ng/mL: Compared to DOAC levels <30 ng/mL, the sensitivity and NPV of the TG parameters were lower and the specificity and PPV higher to predict DOAC levels < 50 ng/mL.

The sensitivity, specificity, PPV, and NPV of the TG parameters' lag time, TTP, peak thrombin, and velocity index within the normal range to predict DOAC levels < 30 ng/mL are shown in Table 2 and for DOAC levels <50 ng/mL in Table S1.

The average detection limit was <10 ng/mL for TTP, peak thrombin, and velocity index in patients taking edoxaban and rivaroxaban. In apixaban-treated patients, the average detection limit was lowest for TTP and velocity index and in dabigatran-treated for lag time.

The maximum detection limit was <30 ng/mL in patients under rivaroxaban for lag time, TTP, and velocity index. In edoxaban-treated patients, the maximum detection limit of all TG values was 63.2 ng/mL, which was caused by one outlier. After exclusion of this outlying value, the maximum detection limit in patients under edoxaban was 32.1 ng/mL for TTP, peak thrombin, and velocity index and 15.6 ng/mL for lag time. The average and maximum detection limits of lag time, TTP, peak thrombin, and velocity index are shown in Table 3.

4 | DISCUSSION

In this study, we analyzed 380 plasma samples from a real-world population of DOAC treated patients. We were able to show a correlation between the plasma levels of the anti-Xa DOACs edoxaban and rivaroxaban (r^2 > .61) as well as apixaban (r^2 > .49) and the TG parameters' lag time, peak thrombin, TTP, and velocity index. In contrast, only lag time and TTP showed a significant correlation with plasma levels of dabigatran. This effect of dabigatran on TG is in accordance with findings from a study with dabigatran spiked plasma samples using the CAT system after the dabigatran antidote idarucizumab was added to the calibration well to overcome the inhibitory effect of dabigatran on the α_2-macroglobulin-thrombin–based calibrator.[16] While using CAT, sample plasma in the calibrator well runs together with the same sample plasma in the measurement well. When dabigatran is present in the sample plasma, the calibrator is inhibited and the calculated thrombin is too high.[17] In

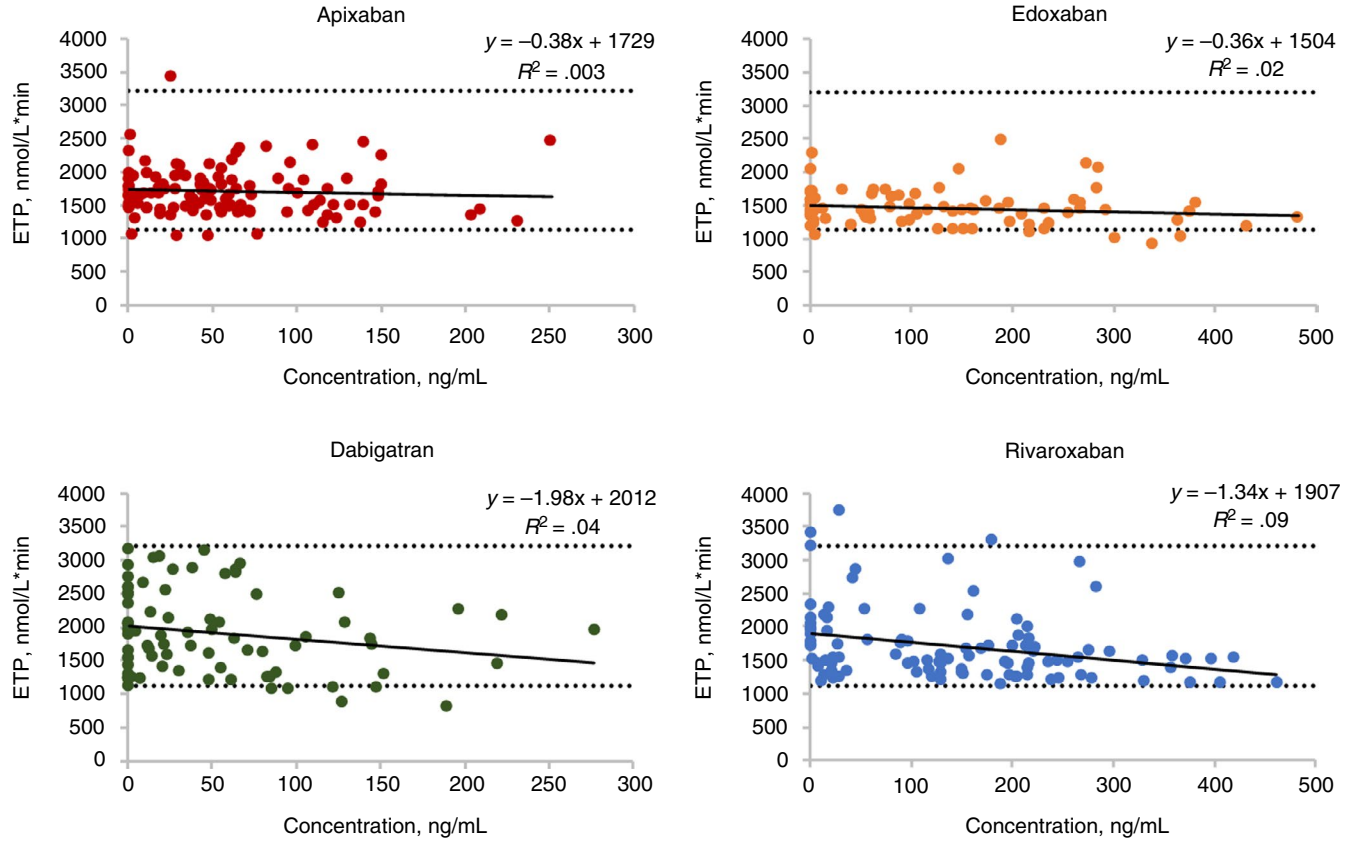

FIGURE 4 Correlation between direct oral anticoagulant (DOAC) concentrations and endogenous thrombin potential (ETP). Solid line: regression curve; dotted lines: 2.5th and 97.5th percentile of 42 untreated patients

contrast, buffered human thrombin instead of α_2-macroglobulin-thrombin complex is used in ST Genesia for daily calibration, and the calibrator does not come in contact with patient plasma. Therefore, dabigatran-induced calibration errors are avoided in ST Genesia.

Regarding anti-Xa inhibitors, thrombin peak and lag time seem to be best correlated with apixaban[18] and edoxaban[19] drug levels in spiked plasma samples, while the effect of these drugs on ETP is less pronounced and can be enhanced when thrombomodulin was added to the assay.[18] In a crossover study in healthy volunteers taking apixaban 2 × 5 mg and rivaroxaban 1 × 20 mg, TG assessed using CAT showed a higher inhibition of peak thrombin and lag time with rivaroxaban treatment compared to apixaban.[20] In that study, DOAC treatment led to a decrease in ETP that was less pronounced than the inhibition of peak thrombin. The same effect was shown with ST Genesia and the STG-DrugScreen reagent in 17 healthy volunteers after a single dose of 40 mg rivaroxaban.[13] Another study on 10 healthy male volunteers after a single dose of dabigatran, rivaroxaban, and apixaban using the CAT system revealed a high correlation for lag time, peak thrombin, TTP, and velocity index with apixaban and rivaroxaban drug levels, while the highest correlation for dabigatran was found with lag time and to a lesser extent with TTP. ETP showed a poor correlation with all tested DOACs.[21] Our study has shown similar results in a large cohort of patients using a fully automated TGA.

There are currently very limited data about the comparability of the ST Genesia with the CAT system. Two recent publications compared CAT with STG-BleedScreen (BLS) and STG-ThromboScreen (TS). TG parameters obtained with CAT using blood samples from patients undergoing liver transplant showed different results compared to those with ST Genesia BLS and TS.[22] In contrast, in another study on healthy volunteers, BLS showed a positive correlation with peak thrombin and ETP in CAT using 1 pM tissue factor, while TS correlated only with peak thrombin in CAT with 5 pM TF in the absence of thrombomodulin and with ETP in the presence of thrombomodulin.[23] Comparisons between the STG-DrugScreen reagent with classical TG regarding the sensitivity of both methods are difficult to perform. Most studies reported TG data from healthy volunteers after DOAC intake[20,21] or in spiked plasma samples.[18,19] We included patients treated with DOACs who were older and had higher baseline ETP and thrombin peak levels than the healthy volunteers reported by Artang and colleagues,[21] making a direct comparison of the applied methods unfeasible.

In conclusion, TG parameters' lag time, peak thrombin, TTP, and velocity index assessed with ST Genesia correlate with drug levels of anti-Xa DOACs. For dabigatran-treated patients, only lag time has a correlation with the dabigatran plasma levels.

In addition, we assessed reference ranges using TG parameters of 42 previously untreated patients and used these reference ranges for the calculation of sensitivity and specificity of the TG parameters to predict DOAC levels below 30 and 50 ng/mL. The sensitivity of a normal lag time and a normal peak thrombin to predict DOAC

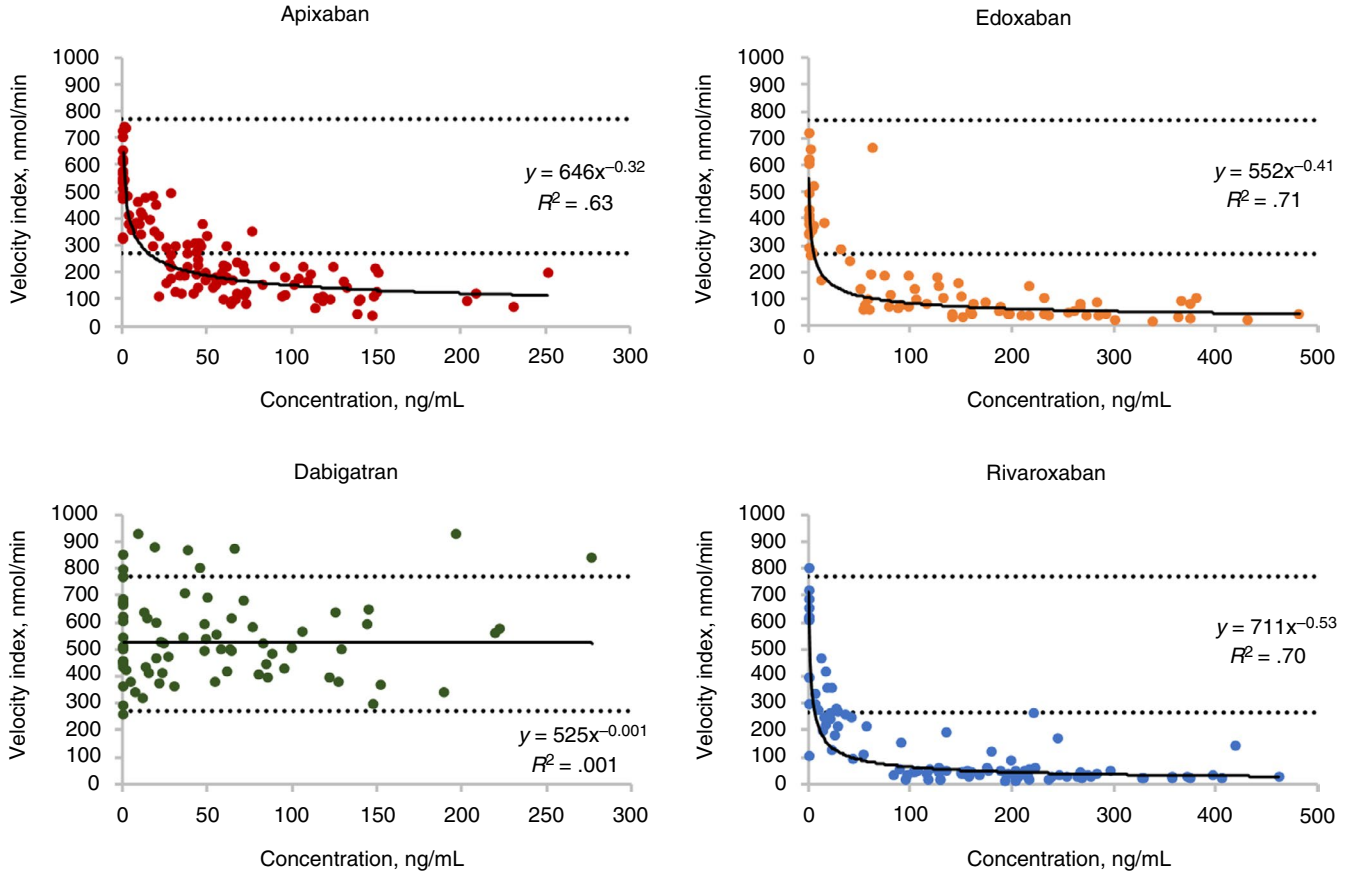

FIGURE 5 Correlation between direct oral anticoagulant (DOAC) concentrations and thrombin generation velocity index. Solid line: regression curve; dotted lines: 2.5th and 97.5th percentile of 42 untreated patients

TABLE 1 Spearman correlation (r^2) between DOAC drug levels and thrombin generation parameters

	Lag time	Peak thrombin	TTP	ETP	Velocity index
Apixaban, n = 120					
r^2	.49	.53	.61	.003	.63
P value	<.001	<.001	<.001	.116	<.001
Dabigatran, n = 79					
r^2	.60	.04	.43	.04	.001
P value	<.001	.09	<.001	.12	.76
Edoxaban, n = 79					
r^2	.62	.61	.78	.02	.71
P value	<.001	<.001	<.001	.17	<.001
Rivaroxaban, n = 102					
r^2	.70	.65	.74	.09	.69
P value	<.001	<.001	<.001	.001	<.001

levels <30 ng/mL was >80% for all DOACs, but the specificity was >80% only for edoxaban and rivaroxaban. The highest PPV (>90%) for DOAC levels <30 ng/mL was found for a normal lag time, TTP, and velocity index in edoxaban- and rivaroxaban-treated patients, while PPV was lower in apixaban-treated patients. The reason for these lower values is not clear and might be due to the different molecular structure of apixaban. However, in a direct comparison between rivaroxaban and apixaban in healthy volunteers, it has been shown that the effects of apixaban but not rivaroxaban on the TG parameter lag time and TTP in some individuals was smaller than expected on the basis of the plasma concentrations.[20] For dabigatran, the sensitivity of all TG parameters was >89%, but the PPV and the specificity were poor. Nevertheless, the NPV of all combinations of TG parameters and DOACs, except dabigatran and velocity index, for DOAC levels <30 mg/mL was >85%. This implies that the drug level at which all TG parameters were outside the reference range was, with some exceptions, higher than 30 ng/mL. This raises the question on which hemostatic assay is the best to predict the real hemostatic potential of the patient.

As the individual variation of DOAC peak and trough levels is high, there is a need for a global hemostatic test with defined target values to guide clinicians through the decision whether to reverse anticoagulation in case of urgent surgery or prior to systemic thrombolysis for acute stroke. This is even more pronounced as andexanet alpha is licensed for the reversal of anti-Xa DOACs in the United States and Europe but at very high costs. However, dose recommendations for andexanet alpha are not based on DOAC plasma levels but on the time interval and applied dose of the anticoagulant. In contrast, the ISTH expert statement recommends antidote administration for serious

TABLE 2 Sensitivity and specificity of thrombin generation parameters within the reference range to predict DOAC levels <30 ng/mL

		Sensitivity		PPV		Specificity		NPV	
Assay	DOAC	n	%	n	%	n	%	n	%
Lag time	Apixaban	36/43	83.7	36/60	60.0	53/77	68.8	53/60	88.3
	Dabigatran	36/39	92.3	36/46	78.3	30/40	75.0	30/33	90.9
	Edoxaban	19/21	90.5	19/20	95.0	57/58	98.3	57/59	96.6
	Rivaroxaban	24/29	82.8	24/24	100	73/73	100	73/78	93.6
TTP	Apixaban	32/43	74.4	32/43	74.4	66/77	85.7	66/77	85.7
	Dabigatran	35/39	89.7	35/55	63.6	20/40	50.0	20/24	83.3
	Edoxaban	19/21	90.5	19/20	95.0	57/58	98.3	57/59	96.6
	Rivaroxaban	19/29	65.5	19/19	100	73/73	100	73/83	88.0
Peak	Apixaban	39/43	90.7	39/58	67.2	58/77	75.3	58/62	93.5
	Dabigatran	38/39	97.4	38/67	56.7	11/40	27.5	11/12	91.7
	Edoxaban	19/21	90.5	19/23	82.6	54/58	93.1	54/56	96.4
	Rivaroxaban	24/29	82.8	24/28	85.7	69/73	94.5	69/74	93.2
Velocity index	Apixaban	37/43	86.0	37/49	75.5	65/77	84.4	65/71	91.5
	Dabigatran	38/39	97.4	38/78	48.7	0/40	0	0/1	0
	Edoxaban	19/21	90.5	19/21	90.5	55/58	96.6	55/58	96.6
	Rivaroxaban	20/29	69.0	20/20	100	73/73	100	73/83	89.0

TABLE 3 Average and maximum detection limit

	Lag time		Time to peak		Peak thrombin		Velocity index	
	Average	Maximum	Average	Maximum	Average	Maximum	Average	Maximum
Apixaban	50.0	124.4	11.8	77.0	21.6	151.3	15.6	77.0
Dabigatran	25.0	100.2	113.6	NA	NA	NA	NA	NA
Edoxaban	25.0	63.2	5.7	63.2	6.4	63.2	5.8	63.2
Rivaroxaban	12.1	29.0	5.5	28.7	10.5	44.5	6.3	29.0

Note: Average: average detection limit, defined as the drug level in nanograms per milliliter at which the regression line crosses the upper limit of normal for lag time and time to peak and the lower limit of normal for peak thrombin and velocity index.

Maximum: maximum detection limit, defined as the drug level in nanograms per milliliter at which all values for lag time and time to peak are below and for peak thrombin and velocity index above the reference range

NA, not applicable.

bleedings in plasma levels exceeding 50 ng/mL and for urgent interventions associated with a high bleeding risk above 30 ng/mL.[15] Our data indicate that DOAC levels >30 ng/mL can be associated with normal TG parameters in some patients, while TG parameters are suppressed at the same plasma levels in others. The sensitivity of TG to predict DOAC plasma levels <30 ng/mL, particularly for rivaroxaban and edoxaban was high. Nevertheless, our data have to be interpreted with caution because of the limited amount of plasma samples included in the study and the lack of a clinical outcome, such as bleeding or thrombotic events. However, in contrast to DOAC plasma levels, TG reflects the individual coagulation status of the patient, which consists of pro- and antithrombotic components including the anticoagulant. Further studies with defined clinical end points are necessary to evaluate a TG-based reversal strategy in DOAC-treated patients.

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AUTHOR CONTRIBUTIONS

CP was responsible for the design of the study, data collection, statistical analysis, and writing the manuscript. MM was responsible for the design of the study, data collection, statistical analysis, and revising the manuscript. AS was responsible for the laboratory analysis and revising the manuscript. TK was responsible for data collection. TS was responsible for the laboratory analysis, statistical analysis, and revising the manuscript. SP was responsible for the design of the study and revising the manuscript. CP and MM contributed equally to this work.

RELATIONSHIP DISCLOSURE

TK reports nothing to disclose. MM reports personal fees from Bayer for speakers/consulting honoraria, personal fees from Boehringer Ingelheim for consulting honoraria, personal fees from Bristol-Myers Squibb/Pfizer for speakers honoraria, and research grants and personal fees from Daiichi Sankyo for consulting honoraria outside the submitted work. SP reports grants and

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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